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PATENT APPLICATION FORM (CONVENTION AND NON-CONVENTION)

Regulation 6

5

COMMONWEALTH OF AUSTRALIA

Patents Act 1952

PATENT OFFICE
$245

APPLICATION FOR A STANDARD PATENT OR A STANDARD PATENT OF ADDITION

AU 86/59.209

(a) BAYER AKTIENGESELLSCHAFT

of (b) D-5090 Leverkusen, Bayerwerk, Germany

hereby apply for the grant of a (c) Standard Patent ~~Patent of Addition~~ for an invention entitled (d)

"Production-promoting agents"

which is described in the accompanying (c) ~~provisional~~ complete specification.

(e) For a Convention application – details of basic application(s) –

NUMBER	COUNTRY	DATE OF APPLICATION
P 35 22 938.1	Germany	27th June 1985

~~For Patent of Addition (Section 73):~~

~~I/We request that the Patent may be granted as a Patent of Addition~~

~~the complete specification for~~ Application No. ~~(f)~~

~~Dated this (g) day of~~

~~I/We request that the grant of the Patent of Addition be~~

~~Yours faithfully~~

~~(h) Signature~~

~~(i) Name~~

~~(j) Address~~

~~(k)~~

~~Commissioner of Patents~~

~~ARTHUR S. CAVE & CO.~~

~~PATENT AND TRADE MARK ATTORNEYS~~

~~SYDNEY~~

~~A.S.C. 1~~

Mr Our address for service is ARTHUR S. CAVE & CO., Patent and Trade Mark Attorneys, 1 Alfred Street, Sydney, New South Wales, Australia 2000.

Dated this (g) 25th day of June 1986

BAYER AKTIENGESELLSCHAFT
By Its Patent Attorneys
ARTHUR S. CAVE & CO.

(h) (Signature)

JAMES G. SIELY, F.I.P.A.A.

(i)

(j) Sydney

(k)

Commissioner of Patents

ARTHUR S. CAVE & CO.
PATENT AND TRADE MARK ATTORNEYS
SYDNEY

A.S.C. 1

CBVT

RETOUR A
DCR - ID / BREVETS

(12) AUSTRALIAN PATENT ABSTRACT (11) AU-A-59209/86
(19) AU

(54) SUBSTITUTED UREAS/THIOUREAS AND ISOUREAS / ISOTHIOUREAS USED AS PRODUCTION PROMOTING AGENTS IN LIVESTOCK

(71) BAYER AKTIENGESELLSCHAFT
(21) 59209/86 (22) 25.6.86 (24) 27.6.85
(31) 3522938 (32) 27.6.85 (33) DE
(43) 8.1.87
(51)[4] C07C 127/19 C07C 127/15 C07C 127/26 C07C 149/43
C07C 157/05 C07C 157/09 C07C 157/14 C07D 333/38
C07D 209/14 C07D 233/64 C07D 333/66 C07D 333/54
A23K 1/16

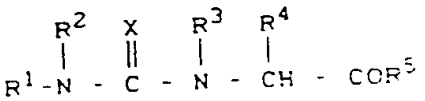
(72) WERNER HALLENBACK, HANS LINDEL, FRIEDRICH BERSCHAUER, MARTIN SCHEER AND ANNO DE JONG

(74) CA

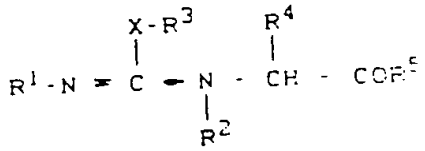
(57) The compounds of formulae Ia and Ib are claimed [illegible]

Claim

1. Use of the substituted ureas and isoureas of the formulae Ia and Ib



Ia



Ib

in which

R^1 stands alkyl, monocyclic or polycyclic cycloalkyl, cycloalkanone, aryl, heteroaryl, alkenyl, cycloalkenyl or cycloalkenoxy, each of which can optionally be substituted,

R^2 represents hydrogen or alkyl,
R^3 represents hydrogen or alkyl,
R^4 represents alkyl which can optionally be substituted,
R^3 and R^4 can, together with the atoms to which they are bonded, form an optionally substituted 5-membered saturated ring,
R^5 represents OH, alkyl, alkoxy, aryl or aryloxy, each of which can be optionally substituted, amino, $-NR^6R^7$,
R^6 represents hydroger or alkyl,
R^7 represents hydrogen, alkyl, alkenyl, alkynyl, aryl or aralkyl, each of which can be optionall, substituted,
X represents O or S,

as production-promoting agents for livestock.

The active compounds of the formulae Ia and Ib can, in this context, be in the form of their enantiomers and in the form of their physiologically tolerated salts.

6. Growth-promoting agents for livestock, characterized by containing substituted ureas and isoureas of the formulae Ia and Ib according to Claim 1.

7. Feed and feed additives for livestock, characterized by containing substituted ureas and isoureas of the formulae Ia and Ib according to Claim 1.

COMMONWEALTH OF AUSTRALIA

Form 10
Regulation
13(2)

PATENTS ACT, 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

Short Title:

Int. Cl:

Application Number: 59209/86

Lodged:

Complete Specification-Lodged:
Accepted:
Lapsed:
Published:

Priority:

Related Art:

TO BE COMPLETED BY APPLICANT

Name of Applicant: BAYER AKTIENGESELLSCHAFT

Address of Applicant: D-5090 Leverkusen, Bayerwerk, Germany

Actual Inventor: Werner HALLENBACK, Hans LINDEL, Friedrich BERSCHAUER, Martin SCHEER and Anno de JONG

Address for Service: ARTHUR S. CAVE & CO., Patent and Trade Mark Attorneys, 1 Alfred Street, Sydney, New South Wales, Australia, 2000.

Complete Specification for the invention entitled:

"Production-promoting agents"

The following statement is a full description of this invention, including the best method of performing it known to me:-

---

ASC-49

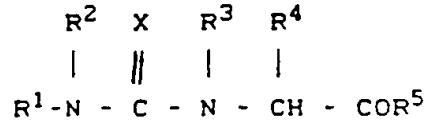
The present invention relates to the use of substituted ureas and isoureas, some of which are known, as production-promoting agents for livestock, to new substituted ureas, and to process for their preparation.

Substituted ureas and their use as herbicides have already been disclosed. (DE-OS (German Published Specification) 3,236,626). Monosubstituted ureas and their use as feed additives for poultry and non-ruminants have already been disclosed (DE-OS (German Published Specification) 1,807,604). Ureas substituted by acetic acid, and their use as production-promoters in livestock have already been disclosed (DE-OS (German Published Specification) 2,501,788, DE-OS (German Published Specification) 2,505,301).

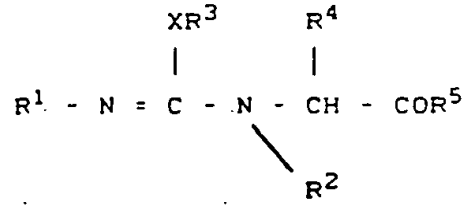
In the case of the known compounds, either nothing is known about their suitability as production-promoters in livestock or their action is not entirely satisfactory.

The present invention relates to:

1. The use of substituted ureas and isoureas, some of which are known, of the formulae Ia and Ib



Ia



Ib

in which

R^1 stands alkyl, monocyclic or polycyclic cycloalkyl, cycloalkanone, aryl, heteroaryl, alkenyl, cycloalkenyl or cyloalkenone, each of which can optionally be substituted,

R^2 represents hydrogen or alkyl,

R^3 represents hydrogen or alkyl,

R^4 represents akyl which can optionally be substituted,

R^3 and R^4 can, together with the atoms to which they are bonded, form an optionally substituted 5-membered saturated ring,

R^5 represents OH, alkyl, alkoxy, aryl or aryloxy, each of which can be optionally substituted, amino, $-NR^6R^7$,

R^6 represents hydrogen or alkyl,

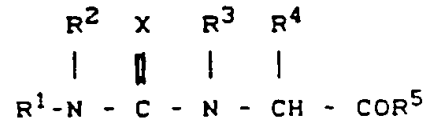
R^7 represents hydrogen, alkyl, alkenyl, alkynyl, aryl or aralkyl, each of which can be optionally substituted,

X represents O or S,

as production-promoting agents for livestock.

The active compounds of the formulae Ia and Ib can, in this context, be in the form of their enantiomers and in the form of their physiologically tolerated salts.

2. Substituted ureas of the formula Ia



Ia

in which

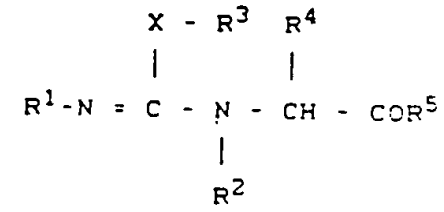
R^1 represents alkyl, one or polycyclic cycloalkyl, cycloalkanone, alkenyl, cycloalkenyl, cycloalkenone, naphthyl or thiophene, each of which can optionally be substituted,

R^2 represents hydrogen or alkyl,

R^3 represents hydrogen or alkyl,
R^4 represents substituted alkyl,
R^5 represents alkyl, alkoxy, arly or aryloxy, each of which can be optionally substituted, or represents amino or $-NR^6R^7$,
R^6 represents hydrogen or alkyl,
R^7 represents hydrogen, alkyl, alkenyl, alkynyl, aryl or aralkyl, each of which can be optionally substituted,
X represents O or S,

are new.

3. Substituted isoureas of the formula Ib



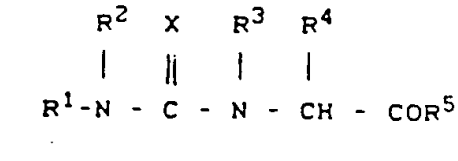
Ib

in which

R^5 represents alkyl, alkoxy, aryl, aryloxy, each of which can be optionally substituted, or represents amino or $-NR^6R^7$,
R^1, R^2, R^3, R^4, R^6, R^7 and X have the meaning indicated under 1 (above)

are new.

4. Process for the preparation of substituted ureas of the formula Ia



Ia

in which

R^1 represents alkyl, one or polycyclic cycloalkyl, cycloalkanone, alkenyl, cycloalkenyl, cycloalkenone, naphthyl or thiophene, each of which can optionally be substituted,

R^2 represents hydrogen or alkyl,
R^3 represents hydrogen or alkyl,
R^4 represents substituted alkyl,
R^5 represents alkyl, alkoxy, aryl or aryloxy, each of which can be optionally substituted, or represents amino or $-NR^6R^7$,
R^6 represents hydrogen or alkyl,
R^7 represents hydrogen, alkyl, alkenyl, alkynyl, aryl or aralkyl, each of which can be optionally substituted,
X represents O or S,

characterized in that

a) in the case where R^2 represents hydrogen, isocyanates or isothiocyanates of the formula II

$$R^1\text{-}NCO(S) \qquad II$$

in which

R^1 has the abovementioned meaning,

are reacted with amino acid derivatives of the formula III

$$HN - \underset{\displaystyle R^4}{\underset{|}{CH}} - \underset{\displaystyle R^3}{\underset{|}{CO}}R^5 \qquad III$$

in which

R^3, R^4 and R^5 have the abovementioned meaning, where appropriate in the presence of catalysts and diluents, or

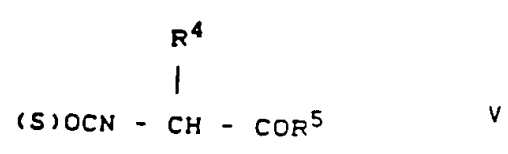
b) in the case where R^3 represents hydrogen, amines of the formula IV

$$R^1 - \underset{\displaystyle R^2}{\underset{|}{N}} - H \qquad IV$$

in which

R^1 and R^2 have the abovementioned meaning,

are reacted with isocyanates or isothiocyanates of the formula V



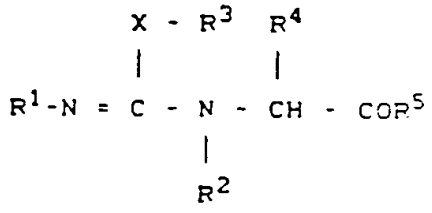
V

in which

R^4 and R^5 have the abovementioned meaning,

where appropriate in the presence of catalysts and diluents.

5. Process for the preparation of substituted isoureas of the formula Ib



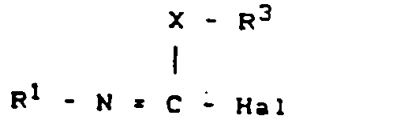
Ib

in which

R^5 represents alkyl, alkoxy, aryl, aryloxy, each of which can be optionally substituted, or represents amino or $-NR^6R^7$,

R^1, R^2, R^3, R^4, R^6, R^7 and X have the meaning indicated under 1 (above)

characterized in that imidocarbonic ester halides of the formula VI



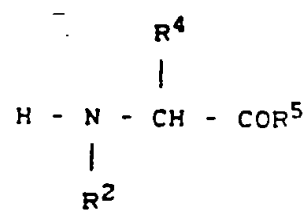
VI

in which

Hal represents halogen,

X, R^1 and R^3 have the abovementioned meaning,

are reacted with amino acid derivatives of the formula VII



VII

in which

R^2, R^4 and R^5 have the abovementioned meaning.

The substituted ureas and isoureas of the formulae Ia and Ib have a considerably better production-promoting action in livestock than do the urea derivatives for which an action of this type has hitherto been known.

The substituted ureas and isoureas which are preferably used are those of the formulae Ia and Ib in which

R^1 represents C_{1-12}-alkyl, C_{3-10}-cycloalkyl, C_{5-6}-cycloalkanone, adamantyl, phenyl, naphthyl, heteroaryl having 5-6 ring atoms, the hetero atoms which can be contained being N, O and S, in particular thiophene and hydrobenzothiophene, C_{2-12}-alkenyl and C_{5-8}-cycloalkenyl, each of which can optionally have one or more of the following identical or different radicals as substituents: alkyl, preferably having 1 to 4, in particular 1 or 2, carbon atoms, such as methyl, ethyl, n- and i.-propyl and n.-, i.- and t.-butyl; fused-on C_{2-5}-alkanyl or C_4-alkenyl; alkoxy, preferably having 1 to 4, in particular 1 or 2, carbon atoms, such as methoxy, ethoxy, n.- and i.-propyloxy and n.-, i.- and t.-butyloxy; alkylthio, preferably having 1 to 4, in particular 1 or 2, carbon atoms, such as methylthio, ethylthio, n.- and

i.-propylthio and n.-, i.- and t.-butylthio; halogenoalkyl, preferably having 1 to 4, in particular 1 or 2, carbon atoms and preferably 1 to 5, in particular 1 to 3, halogen atoms, the halogen atoms being identical or different and as halogen atoms, preferably fluorine, chlorine or bromine, in particular fluorine stand, such as trifluoromethyl; hydroxyl; halogen, preferably fluorine, chlorine, bromine and iodine, in particular chlorine and bromine; cyano; nitro; amino; monoalkylamino and dialkylamino, preferably having 1 to 4, in particular 1 or 2, carbon atoms per alkyl group, such as methylamino, methyl-ethyl-amino, n.- and i.-propylamino and methyl-n.-butylamino; carbalkoxy, preferably having 2 to 4, in particular 2 or 3, carbon atoms, such as carbomethoxy and carboethoxy; alkylsulphonyl, preferably having 1 to 4, in particular 1 or 2, carbon atoms, such as methylsulphonyl and ethylsulphonyl; arylsulphonyl, preferably having 6 or 10 aryl carbon atoms, such as phenylsulphonyl; phenyl, naphthyl, phenoxy, naphthoxy, phenylthio and naphthylthio, which in turn can again be substituted.

Substituents on aromatic rings can additionally be optionally halogen-substituted alkylenedioxy, in particular optionally chlorine- or fluorine-substituted methylenedioxy or ethylenedioxy.

R^2 represents hydrogen or C_{1-4}-alkyl,

R^3 represents hydrogen or C_{1-4}-alkyl,

R_4 represents C_{1-4}-alkyl which can optionally be substituted by aryl, in particular phenyl, OH, SH, C_{1-4}-alkylthio, COOH; $CONH_2$, $COOC_{1-4}$-alkyl, heteroaryl, in particular imidazolyl, indolyl, benzofuranyl and benzothienyl,

R^3 and R^4 can, in the case of the ureas of the formula Ia, form, together with the atoms to which they are bonded, a 5-membered saturated ring which is optionally substituted by OH,

R^5 represents OH, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenyl or phenoxy, each of which can optionally be substituted by one or more of the following identical or different substituents: halogen, CN, C_{1-4}-alkyl, C_{1-4}-alkoxy, phenyl, phenoxy and phenylthio, each of which can in turn be substituted, and represents NH_2 or NR^6R^7,

R^6 represents hydrogen or C_{1-4}-alkyl,

R^7 represents hydrogen, C_{1-4}-alkyl, C_{2-4}-alkenyl, C_{2-4}-alkynyl, phenyl, naphthyl and C_{1-2}-alkylphenyl, each of which can optionally be substituted by halogen, CN, C_{1-4}-alkyl and C_{1-4}-alkoxy, and

X represents O or S.

Compounds of the formula Ia and Ib which are particularly preferably used are those in which

R^1 represents C_{1-4}-alkyl, C_{3-6}-cycloalkyl, polycyclic cycloalkyls such as, for example, adamantyl, furthermore phenyl, naphthyl, heteroaryl having 5-6 ring atoms, in particular thiophene, pyrrole and furan, each of which can optionally be fused onto further cyclic saturated or unsaturated 5 to 7 membered ring, C_{2-6}-alkenyl, cyclopentyl and cyclohexenyl, it being possible for these radicals to be substituted by one or more of the following substituents: alkyl preferably having 1 to 4, in particular 1 or 2, carbon atoms, such as methyl, ethyl, n.- and i.-propyl and n.-, i.- and t.-butyl; fused-on C_{2-4}-alkenyl or C_4-alkenyl; alkoxy preferably having 1 to 4, in particular 1 or 2, carbon atoms, such as methoxy, ethoxy, n.- and i.-propyloxy and n.-, i.- and t.-butyloxy; alkylthio preferably having 1 to 4, in particular 1 or 2, carbon atoms, such as methylthio, ethylthio, n.- and i.-propylthio and n.-,i.- and t.-butylthio;

halogenoalkyl preferably having 1 to 4, in particular 1 or 2, carbon atoms and preferably 1 to 5, in particular 1 to 3, halogen atoms, the halogen atoms being identical or different and as halogen atoms, preferably fluorine, chlorine or bromine, in particular fluorine stand, such as trifluoromethyl; hydroxyl; halogen, preferably fluorine or chlorine, in particular chlorine; cyano; nitro; amino; monoalkylamino and dialkylamino preferably having 1 to 4, in particular 1 or 2, carbon atoms per alkyl group, such as methylamino, methyl-ethyl-amino, n.- and i.-propylamino and methyl-n.-butylamino; carbalkoxy preferably having 2 to 4, in particular 2 or 3, carbon atoms, such as carbomethoxy and carboethoxy; alkylsulphonyl preferably having 1 to 4 , in particular 1 or 2, carbon atoms, such as methylsulphonyl and ethylsulphonyl; arylsulphonyl preferably having 6 or 10 aryl carbon atoms, such as phenylsulphonyl; phenyl.

R^2 represents hydrogen,

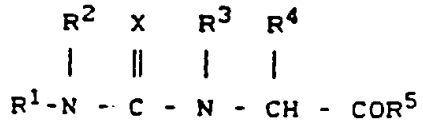
R^3 represents hydrogen,

R^4 represents methyl or ethyl each of which can optionally be substituted by OH or SCH_3, phenyl, hydroxyphenyl, COO C_{1-4}-alkyl, $CONH_2$, imidazolyl or indolyl,

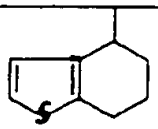
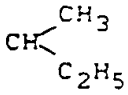
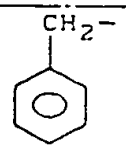
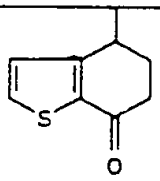
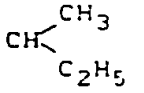
R^5 represents OH, C_{1-4}-alkoxy, in particular methoxy and ethoxy, amino and monoalkylamino, in particular methylamino and ethylamino, and

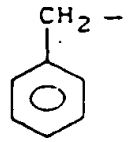
X represents O and S.

Apart from the compounds mentioned in the examples, the following substituted ureas of the formula Ia may be specifically mentioned:

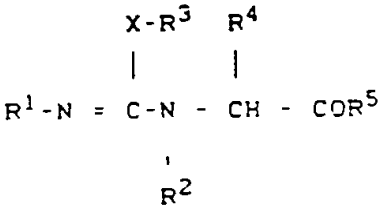


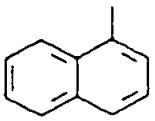
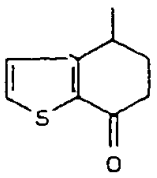
R^1 = H, X = O, R^3 = H, R^5 = OMe

R^2	R^4
	CH_3
ditto	$CH(CH_3)_2$
ditto	
ditto	
ditto	$-CH_2-CH_2-S-CH_3$
	CH_3
ditto	$CH(CH_3)_2$
ditto	

R^2	R^4
ditto	
ditto	$-CH_2-CH_2-S-CH_3$

Apart from the compounds mentioned in the examples, the following substituted isoureas of the formula Ib may be specifically mentioned:



R^1	R^2	X	R^3	R^4	R^5
	H	O	CH_3	$-CH_2-CH_2-S-CH_3$	OCH_3
	H	O	CH_3	$-CH_2-CH_2-S-CH_3$	OCH_3

Of the new substituted ureas, those of the formula Ia which are preferred are those in which

R^1 represents C_1-$_4$-alkyl, one or polycyclic C_5-C_{10}-cycloalkyl, C_5-C_7-cycloalkanone, C_2-C_6-alkenyl, C_6-C_{10}-cycloalkenyl, C_5-C_7 cycloalkenone, naphthyl or thiophene, each of which can optionally be substituted,

R^2 represents hydrogen or C_1-C_4-alkyl,

R^3 represents hydrogen or C_1-C_4-alkyl,
R^4 represents substituted C_1-C_3-alkyl,
R^5 represents C_1-C_4-alkyl, C_1-C_4-alkoxy, aryl or aryloxy, each of which can optionally be substituted, or represents amino or $-NR^6R^7$,
R^6 represents hydrogen or C_1-C_4-alkyl,
R^7 represents hydrogen, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, aryl or C_1-C_4-aralkyl, each of which can optionally be substituted, and
X represents O or S.

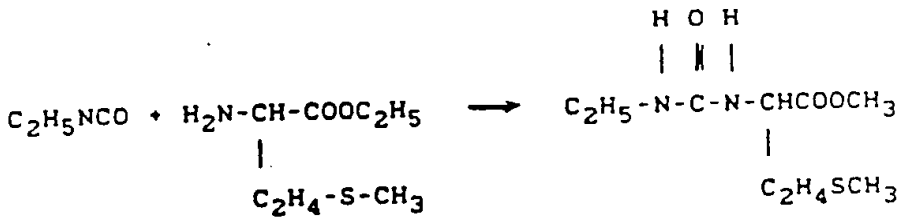
Of the new substituted isoureas, those of the formula Ib which are preferred are those in which the radicals R^1, R^2, R^3, R^4 and X have the meanings indicated as preferred for the new substituted ureas of the formula Ia, and the radical R^5 represents C_1-C_4-alkyl, C_1-C_4-alkoxy, aryl or aryloxy, each of which can optionally be substituted.

The following acids which can form salts with the active compounds of the formula I may be mentioned as preferred:
HCl, H_2SO_4, HSO_4^-, H_3PO_4, $H_2PO_4^-$ $HClO_4$, HBr, HI, HF, HNO_3, H_2CO_3, HCO_3^-, H_3BO_3, HN_3, acetic acid, oxalic acid, malonic acid, succinic acid, malic acid, tartaric acid, maleic acid, fumaric acid, methanesulphonic acid, benzoic acid, substituted benzoic acids, formic acid, chloroacetic acid, toluenesulphonic acid, benzenesulphonic acid, trichloroacetic acid, phthalic acid, naphthalenesulphonic acid, nicotinic acid, citric acid and ascorbic acid.

In the case where R^5 = OH, the following bases which can form salts with the active compounds of the formula I may be mentioned:
NaOH, KOH, alkali and alkaline earth metal carbonates, organic bases such as, for example, triethylamine, mono-alkylamines and dialkylamines, and quaternary ammonium

hydroxides.

The processes indicated at 4 (above) for the preparation of the new substituted ureas of the formula Ia are carried out by reacting the appropriate amines of the formula III or IV with the appropriate isocyanates. When, for example, ethyl isocyanate and methionine ethyl esters are used, the course of the reaction can be represented by the following scheme:



The isocyanates or isothiocyanates of the formulae II and V which are used in processes 4a and b are known or can be prepared in analogy to known methods.

The compounds of the formulae II and V which are preferably used are those which lead to the new active compounds which are mentioned above as being preferred.

Specifically, isocyanates or isothiocyanates of the formula II which are derived from the following amines may be mentioned:
methylamine, ethylamine, propylamine, isopropylamine, butylamine, iso-butylamine, tert.-butylamine, hexylamine, dodecylamine, 2-ethylhexylamine, tetradecylamine, hexadecylamine, octadecylamine, 3-butoxypropylamine, 2-methylpropyl 3-aminopropanoate, 6-aminohexanitrile, 1,1-aminoundecanoic esters, cyclohexylamine, trimethylcyclohexylamine, 2-norbornylmethylamine, aniline, o,m,p-chloroaniline, 2,3-, 2,4-, 2,5- and 2,6-dichloroaniline, 3,4- and 3,5-dichloroaniline, p-, o-nitroaniline, m,o,p-tolylamine, 3-trifluoromethylaniline, 3-chloro-4-methylaniline, 4-chloro-3-methylaniline, benzylamine, phenylcyclohexylamine, naphthylamine, adamantylamine,

additionally 2-amino-3-carbethoxythiophene, 3-amino-2-carbethoxythiophene, 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzothiophene, 2-amino-3-carbethoxy-4,5-dimethylthiophene and 2-amino-3-carbethoxy-4-methyl-5-phenylthiophene.

Specifically, the following isocyanates or isothiocyanates of the formula V may be mentioned: (prepared by the method of P. Stelzel in Methoden der organ. Chemie (Methods of Organ. Chemistry) (Houben-Weyl-Müller) volume XV/2, page 183, published by Georg Thieme Stuttgart).

Methyl 2-isocyanatopropionate, methyl 2-isocyanato-3-methylbutyrate, methyl 2-isocyanato-4-methyl-valerionate, methyl 2-isocyanato-3-phenyl-propionate and methyl 2-isocyanato-3-methyl-pentanoate.

The amines or amino acid derivatives of the formulae III and IV used in processes 4a and b are known or can be prepared in analogy to known methods.

The compounds of the formulae III and IV which are preferably used are those which lead to the new active compounds which are mentioned above as being preferred.

Amines which are listed above may be mentioned as amines of the formula IV.

The processes 4a and 4b are, where appropriate, carried out in the presence of diluents and of catalysts.

Suitable diluents are all inert organic solvents. These include, in particular, aliphatic and aromatic, optionally halogenated, hydrocarbons, such as pentane, hexane, heptane, cyclohexane, petroleum ether, benzine, ligroin, benzene, toluene, methylene chloride, ethylene chloride, chloroform, carbon tetrachloride, chlorobenzene and o-dichlorobenzene, furthermore ethers, such as diethyl and dibutyl ether, glycol dimethyl ether and diglycol dimethyl ether, tetrahydrofuran and dioxane, in addition ketones, such as acetone, methyl ethyl,

methyl isopropyl and methyl isobutyl ketone, additionally esters, such as methyl and ethyl acetate, furthermore nitriles such as, for example, acetonitrile and propionitrile, benzonitrile, glutaric acid dinitrile, moreover amides such as, for example, dimethylformamide, dimethylacetamide and N-methylpyrrolidone, as well as dimethyl sulphoxide, tetramethylene sulphone and hexamethylphosphoric triamide and pyridine.

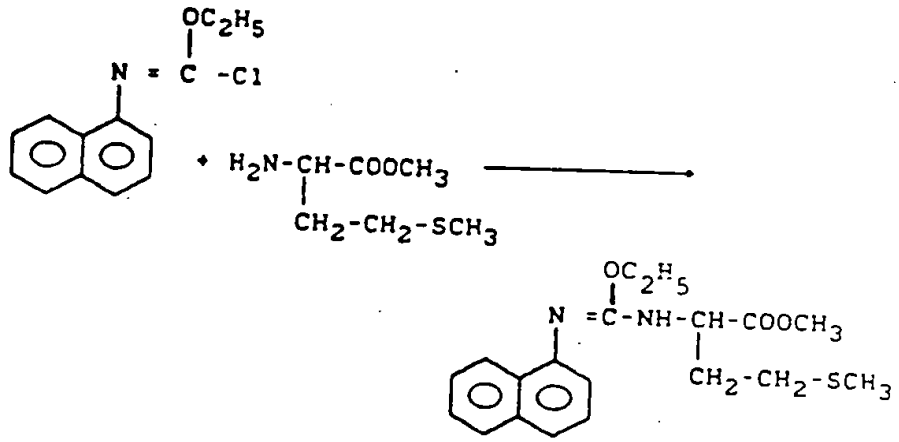
Suitable catalysts are the catalysts customary for reactions with isocyanates. The following may be mentioned: tert.-amines, such as triethylamine, N-methylmorpholine, 1,4-diaza-bicyclo-(2,2,2)-octane (DABCO), β,β'-dimethylaminodiethyl ether and dimethylbenzylamine, metal catalysts of Zn, Sn and Pb, such as dibutyltin dilaurate, dibutyltin dioxide, tin octoate, lead octoate, zinc octoate, zinc chloride, zinc acetate, 4-dimethylaminopyridine.

The reaction is carried out between 50 and 150°C, preferably between 60-110°C. It is preferably carried out under atmospheric pressure.

The compounds of the formulae II and III or IV and V are used in equimolar amounts, a small excess of one or other of the components entails no essential advantages.

The working-up is carried out in a manner known per se, for example by addition of water to the reaction mixture, removal of the organic phase and removal of the solvent by distillation.

Isoureas of the formula Ib can be prepared from the appropriate amino acid derivatives of the formula VII by reaction with the appropriate imidocarbonic ester halides of the formula VI When 1-naphthyl-imidocarbonic ethyl ester chloride and methionine methyl ester are used, the course of the reaction can be represented by the scheme below:



The amino acid derivatives of the formula VII which are preferably used are those which lead to the compounds of the formula Ib which are mentioned above as being preferred.

Imidocarbonic ester halides are known or can be prepared in analogy to known methods. The compounds of the formula VI which are preferably used are those which lead to the new active compounds which are mentioned above as being preferred.

Halogen represents, in particular, chlorine.

Specifically, the following imidocarbonic ester halides of the formula VI may be mentioned: methyl ethyliminochlorocarbonate, ethyl cyclohexyliminochlorocarbonate and methyl 1-naphthyliminochlorocarbonate. Preparation: E. Kühle in Methoden der Organischen Chemie (Houben-Weyl-Müller) vol. E4, page 544, published by Thieme, Stuttgart 1983.

The reaction is carried out, where appropriate, in the presence of acid acceptors, catalysts and diluents.

The compounds of the formula VI and VII are preferably used in equimolar amounts. An excess of one or other of the components entails no essential advantage.

Suitable diluents are all inert organic solvents. These include, in particular, aliphatic and aromatic, optionally halogenated, hydrocarbons, such as pentane, hexane, heptane, cyclohexane, petroleum ether, benzine, ligroin, benzene, toluene, methylene chloride, ethylene chloride, chloroform, carbon tetrachloride, chlorobenzene and o-dichlorobenzene, furthermore ethers, such as diethyl and dibutyl ether, glycol dimethyl ether and diglycol dimethyl ether, tetrahydrofuran and dioxane, in addition ketones, such as acetone, methyl ethyl, methyl isopropyl and methyl isobutyl ketone, additionally esters, such as methyl and ethyl acetate, furthermore nitriles such as, for example, acetonitrile and propionitrile, benzonitrile, glutaric acid dinitrile, moreover amides such as, for example, dimethylformamide, dimethylacetamide and N-methylpyrrolidone, as well as tetramethylene sulphone and hexamethylphosphoric triamide.

All customary acid binding agents can be used as acid acceptors. These preferably include alkali metal carbonates, hydroxides or alcoholates, such as sodium or potassium carbonate, sodium and potassium hydroxide, sodium and potassium methylate and ethylate, also aliphatic, aromatic or heterocyclic amines, for example trimethylamine, triethylamine, tributylamine, dimethylaniline, dimethylbenzylamine and pyridine.

The compounds which can be used as catalysts are those which are customarily used for the phase transfer of reactants in reactions in two-phase systems comprising water and organic solvents which are immiscible with water (phase-transfer catalysts). Those which are particularly preferred are tetraalkyl- and trialkylaralkylammonium salts preferably having 1 to 10, in particular 1 to 8, carbon atoms per alkyl group, preferably phenyl as the aryl constituent of the aralkyl group and preferably 1 to 4, in particular 1 or 2, carbon atoms in the

alkyl moiety of the aralkyl groups. Of these, particularly preferred are the halides, such as chlorides, bromides and iodides, preferably 1 to 4, in particular 1 or 2, carbon atoms in the alkyl moiety of the aralkyl groups. Of these, particularly suitable are the halides, such as chlorides, bromides and iodides, preferably the chlorides and bromides. Examples which may be mentioned are tetrabutylammonium bromide, benzyltriethylammonium chloride and methyltrioctylammonium chloride.

The reaction temperature is maintained between about 0°C and 130°C, preferably between about 20°C and 60°C. The process is preferably carried out under atmospheric pressure.

The working-up is carried out in a customary manner.

The active compounds are used in livestock to promote and accelerate growth, the production of milk and wool, and to improve the feed utilization, the meat quality and to shift the meat/fat ratio in favour of meat. The active compounds are used for useful, breeding, ornamental and hobby livestock.

The useful and breeding livestock include mammals such as, for example, cattle, pigs, horses, sheep, goats, rabbits, hares, fallow deer, fur-bearing livestock such as mink and chinchilla, poultry such as, for example, chickens, geese, ducks, turkeys and pigeons, fish such as, for example, carp, trout, salmon, eels, tench and pike, and reptiles such as, for example, snakes and crocodiles.

The ornamental and hobby animals include mammals such as dogs and cats, birds such such as parrots and canaries, and fish such as ornamental and aquarium fish, for example goldfish.

The active compounds are used irrespective of the sex of the livestock during all phases of growth and

production of the livestock. The active compounds are preferably used during the phase of intensive growth and production. Depending on the species, the phase of intensive growth and production lasts from one month up to 10 years.

The amount of the active compounds which is administered to the livestock to achieve the desired effect can be varied within wide limits because of the favourable properties of the active compounds. It is preferably about 0.001 to 50 mg/kg, in particular 0.01 to 5 mg/kg, of body weight per day. The appropriate amount of the active compound and the appropriate duration of the administration depend, in particular, on the species, the age, the sex, the phase of growth and production, the state of health and the nature of the housing and feeding of the livestock, and can readily be determined by all those skilled in the art.

The active compounds are administered to the livestock by customary methods. The mode of administration depends, in particular, on the species, the behaviour and the state of health of the livestock.

The active compounds can be processed once. However, it is also possible for the active compounds to be administered temporarily or continuously throughout the entire, or throughout a part, of the phase of growth and production.

With continuous administration, the administration can take place once or several times a day, at regular or irregular intervals.

The administration is carried out orally or parenterally, in formulations suitable for this purpose or in the pure form.

The active compounds can be present in the formulations alone or mixed with other production-promoting active compounds, mineral feedstuffs, trace element compounds, vitamins, non-protein compounds, colorants,

antioxidants, flavourings, emulsifiers, flow regulators, preservatives and pelleting auxiliaries.

Other production-promoting active compounds are: for example antibiotics such as tylosin and virginiamycin. Examples of mineral feedstuffs are dicalcium phosphate, magnesium oxide and sodium chloride. Examples of trace element compounds are iron fumarate, sodium iodide, cobalt chloride, copper sulphate and zinc oxide. Examples of vitamins are vitamin A, vitamin D_3, vitamin E, B vitamins and vitamin C. Examples of non-protein compounds are biuret and urea. Examples of colorants are carotenoids such as citranaxanthine, zeaxanthine and capsanthine. Examples of antioxidants are ethoxyquin and butylhydroxy-toluene. Examples of flavourings are vanillin. Examples of emulsifiers are esters of lactic acid, and lecithin. Examples of flow regulators are sodium stearate and calcium stearate. Examples of preservatives are citric acid and propionic acid. Examples of pelleting auxiliaries are lignin-sulphonates and cellulose ethers.

The active compounds can also be administered together with the feed and/or the drinking water.

The feed includes non-compound feedstuffs of vegetable origin, such as hay, roots and cereals by-products, non-compound feedstuffs of animal origin, such as meat, fats, milk products, bonemeal and fish products, the non-compound feedstuffs such as vitamins, proteins, amino acids, for example DL-methionine, and salts such as lime and sodium chloride. The feed also includes supplementary, compound and mixed feedstuffs. These contain non-compound feedstuffs in a composition which ensure a balanced diet with regard to the supply of energy and protein and the supply of vitamins, mineral salts and trace elements.

The concentration of the active compounds in the feed is normally about 0.01-500 ppm, preferably

0.1-50 ppm.

The active compounds can be added as such, or in the form of premixes or feed concentrates, to the feed.

Example for the composition of a chicken rearing feed which contains active compound according to the invention:

200 g of wheat, 340 g of maize, 361 g of soya meal, 60 g of beef tallow, 15 g of dicalcium phosphate, 10 g of calcium carbonate, 4 g of iodized sodium chloride, 7.5 g of vitamin/mineral mix and 2.5 g of active compound premix provide, after careful mixing, 1 kg of feed.

1 kg of feed mix contains the following:

600 I.U. of vitamin A, 100 I.U. of vitamin D_3, 10 mg of vitamin E, 1 mg of vitamin K_3, 3 mg of riboflavin, 2 mg of pyridoxine, 20 mcg of vitamin B_{12}, 5 mg of calcium pantothenate, 30 mg of nicotinic acid, 200 mg of choline chloride, 200 mg of $MnSO_2 \times H_2O$, 140 mg of $ZnSO_4 \times 7H_2O$, 100 mg of $FeSO_4 \times 7H_2O$ and 20 mg of $CuSO_4 \times 5H_2O$.

2.5 g of active compound premix contain, for example, 10 mg of active compound, 1 g of DL-methionine, and the remainder soya bean meal.

Example for the composition of a pig-rearing feed which contains active compound according to the invention:

630 g of feed cereal meal (composed of 200 g of maize, 150 g of barley meal, 150 g of bonemeal and 130 g of wheatmeal), 80 g of fishmeal, 60 g of soya meal, 60 g of cassava meal, 38 g of brewers' yeast, 50 g of vitamin/mineral mix for pigs, 30 g of linseed cake meal, 30 g of maize gluten feed, 10 g of soya oil, 10 g of sugar cane molasses and 2 g of active compound premix (composition, for example, as for chicken feed) provide, after careful mixing, 1 kg of feed.

The feed mixes indicated are designed for the rearing and fattening of, preferably, chickens and pigs,

but they can also be used, in the same or similar composition, for the feeding of other livestock.

Example A

Rat feeding trial

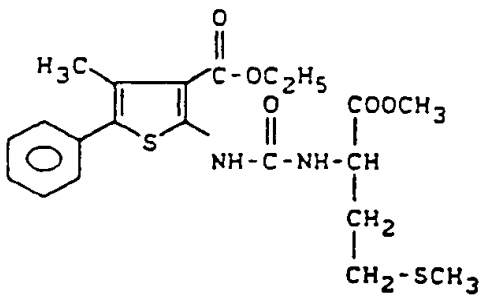
Female laboratory rats weighing 90-110 g of the type SPF Wistar (bred by Hagemann) are fed ad lib. with standard rat feed to which the desired amount of active compound has been added. Each trial arrangement is carried out with feed of the identical batch so that differences in the composition of the feed cannot impair the comparability of the results.

The rats receive water ad lib.

12 rats form each trial group and they are fed with feed to which the desired amount of active compound has been added. A control group receives feed containing no active compound. The mean body weight and the variation in the body weights of the rats are the same in each trial group so that comparability of the trial groups with one another is ensured.

The weight gain and feed consumption during the 13-day trial are determined. The compounds according to the following examples show gain in body weight compared with the control: 1, 2, 3.

Example 1



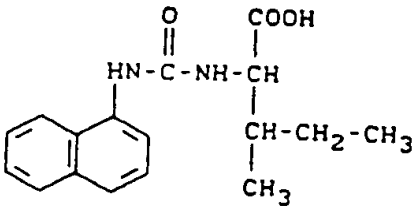
3.4 g (34 mmol) of triethylamine are added to 6.78 g (34 mmol) of L-methionine methyl ester hydrochloride in 30 ml of dry chloroform, and the mixture is

stirred for 10 minutes. Then 6.5 g (22.5 mmol) of 3-carbethoxy-2-isocyanato-4-methyl-5-phenylthiophene, dissolved in 30 ml of dry chloroform, are added dropwise. The reaction is complete after 30 minutes. The mixture is poured onto 300 ml of water, 200 ml of methylene chloride are added, and the organic phase is separated off. The aqueous phase is extracted once more with 150 ml of methylene chloride.

The organic phases are combined and washed successively with 200 ml of dilute sulphuric acid, 200 ml of water and 200 ml of $NaHCO_3$ solution. After drying with Na_2SO_4, the solvent is removed by distillation under reduced pressure, and the product is purified by column chromatography on silica gel using methylene chloride/ethyl acetate as the mobile phase. Yield 7 g (68.7% of theory) of a yellowish oil.

IR: 3450, 3000, 1740, 1660, 1550, 1530 cm^{-1}.

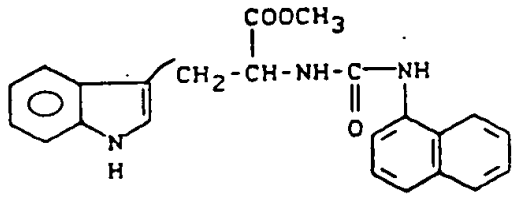
Example 2



2.7 g (25 mmol) of Na_2CO_3 are added to 6.6 g (50 mmol) of L-isoleucine in 50 ml of water. Then a solution of 8.5 g (50 mmol) of 1-naphthyl isocyanate in 10 ml of dioxane is slowly added dropwise to the resulting solution. After completion of the dropwise addition the mixture is stirred for 2 hours then filtered, and the product is precipitated by acidification of the filtrate with formic acid. After filtration with suction and drying over KOH, 6.9 g (46% of theory) of a fine

powder of melting point 171°C (decomposition) are obtained.

Example 3

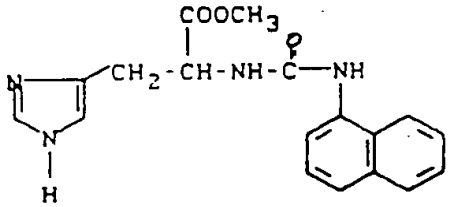


2.54 g (10 mmol) of L-tryptophan methyl ester hydrochloride are suspended in 40 ml of dry chloroform, and 1.01 g (10 mmol) of triethylamine are added. Then a solution of 1.69 g (10 mmol) of 1-naphthyl isocyanate is added dropwise at room temperature, and the reaction mixture is then stirred for 30 minutes. It is subsequently poured into 250 ml of water, the organic phase is separated off, and the aqueous phase is extracted once more with 100 ml of chloroform. The combined organic phases are washed three times with 100 ml of water each time, then dried with Na_2SO_4, and the solvent is evaporated off in vacuo. The residue is recrystallized from toluene/petroleum ether.

Yield 2.5 g (64.6% of theory)

Melting point 188°C.

Example 4



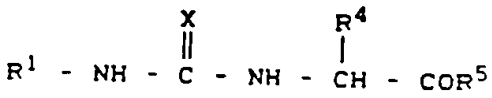
4.2 g (41.4 mmol) of triethylamine are added, and then a solution of 2.8 g (16.6 mmol) of 1-naphthyl

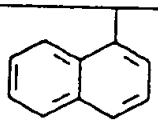
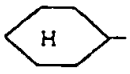
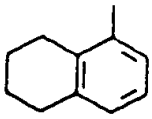
isocyanate in 20 ml of dry chloroform is added dropwise at room temperature, to a suspension of 5 g (20.7 mmol) of L-histidine methyl ester dihydrochloride in 50 ml of dry chloroform. The mixture is then stirred at room temperature for 30 minutes, and subsequently poured onto 200 ml of water, and the precipitated product is filtered off with suction. For purification, it is dissolved in ethanol and precipitated with water.

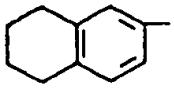
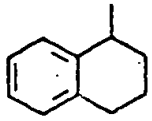
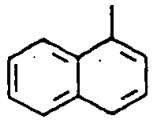
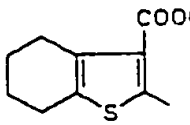
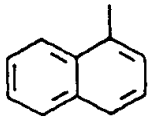
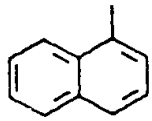
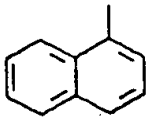
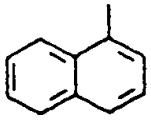
Yield 4.8 g (95% of theory)

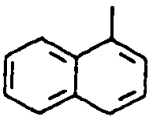
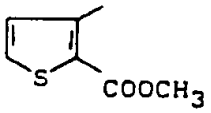
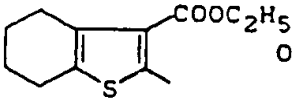
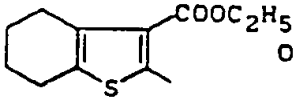
Melting point 132°C (decomposition).

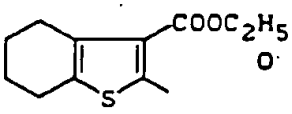
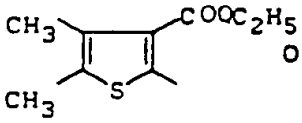
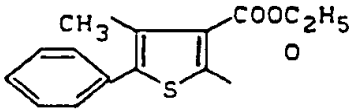
The following compounds are prepared analogously:



Example No.	R^1	X	R^4	R^5	Physic. data M.p. [°C]
5		O	$CH_2CH_2SCH_3$	OCH_3	148
6	i-Propyl	O	"	"	90
7	CH_3	O	"	"	53
8	n-Butyl	O	"	"	45
9		O	"	"	108
10		O	"	"	77
11		O	"	"	137

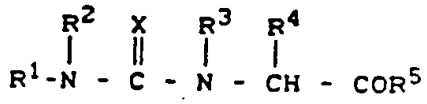
Example No.	R^1	X	R^4	R^5	Physic. data M.p.[°C]
12		O	"	"	78
13					142
14		O	"	OH	168-9
15		O	"	OCH_3	110
16		O	$-CH_2-S-CH_3$	OH	180
17		S	$CH_2CH_2-S-CH_3$	OCH_3	oil
18		S	n-Butyl	OH	156-8
19		O	$CH_2CH_2-S-CH_3$	NH_2	218 (decomc)
20		S	$CH_2CH_2-SCH_3$	NH_2	115 (decomp)

Example No.	R^1	X	R^4	R^5	Physic. data M.p.[°C]
21	Adamantyl	S	$CH_2CH_2SCH_3$	OCH_3	oil
22		O	$CH_2CH(CH_3)_2$	"	112°
23	"	O	$-CH_3$	"	156°
24	"	O	$-C_2H_4-COOCH_3$	"	98°
25	"	O	$-CH_2-OH$	"	193°
26	"	O	$-CHOH-CH_3$	"	201°
27	"	O	$-C_2H_4CONH_2$	OH	206°
28	"	O	$-CH_2-CONH_2$	OH	196°
29	"	O	C_3H_7-i	OCH_3	156°
33		O	$-C_2H_4SCH_3$	"	84°
34		O	$-CH_2OH$	"	119°
35		O	$-CH_2CH(CH_3)_2$	"	103°

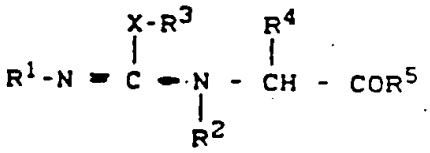
Example No.	R^1	X	R^4	R^5	Physic. data M.p. [°C]
36		O	$-CH_3$	"	98°
37		O	$-C_2H_4SCH_3$	"	Öl
38		O	$-CH_3$	OC_2H_5	54°
39	"	O	$-CH_2OH$	OCH_3	153°
40	"	O	$-CH(CH_3)_2$	"	140°
41	"	O	$-CH_2CH(CH_3)_2$	"	89-91°

~~Patent claims~~ The Claims defining the invention are as follows:

1. Use of the substituted ureas and isoureas of the formulae Ia and Ib



Ia



Ib

in which

R^1 stands alkyl, monocyclic or polycyclic cycloalkyl, cycloalkanone, aryl, heteroaryl, alkenyl, cycloalkenyl or cyloalkenoxy, each of which can optionally be substituted,

R^2 represents hydrogen or alkyl,

R^3 represents hydrogen or alkyl,

R^4 represents alkyl which can optionally be substituted,

R^3 and R^4 can, together with the atoms to which they are bonded, form an optionally substituted 5-membered saturated ring,

R^5 represents OH, alkyl, alkoxy, aryl or aryloxy, each of which can be optionally substituted, amino, $-NR^6R^7$,

R^6 represents hydrogen or alkyl,

R^7 represents hydrogen, alkyl, alkenyl, alkynyl, aryl or aralkyl, each of which can be optionally substituted,

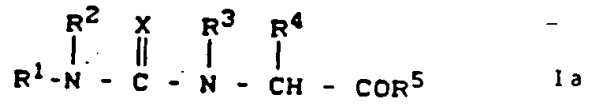
X represents O or S,

as production-promoting agents for livestock.

The active compounds of the formulae Ia and Ib can, in this context, be in the form of their enantio-

mers and in the form of their physiologically tolerated salts.

2. Substituted ureas of the formula Ia



Ia

in which

R^1 represents alkyl, one or polycyclic cycloalkyl, cycloalkanone, alkenyl, cycloalkenyl, cycloalkenone, naphthyl or thiophene, each of which can optionally be substituted,

R^2 represents hydrogen or alkyl,

R^3 represents hydrogen or alkyl,

R^4 represents substituted alkyl,

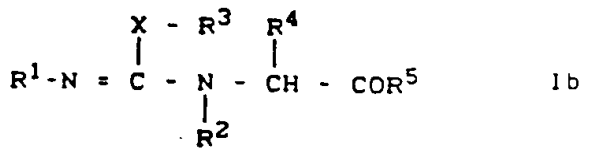
R^5 represents alkyl, alkoxy, aryl or aryloxy, each of which can be optionally substituted, or represents amino or $-NR^6R^7$,

R^6 represents hydrogen or alkyl,

R^7 represents hydrogen, alkyl, alkenyl, alkynyl, aryl or aralkyl, each of which can be optionally substituted,

X represents O or S.

3. Substituted isoureas of the formula Ib



Ib

in which

R^1 represents alkyl, one or polycyclic cycloalkyl, cycloalkanone, alkenyl, cycloalkenyl, cycloalkenone, naphthyl or thiophene, each of which

can optionally be substituted,
R^2 represents hydrogen or alkyl,
R^3 represents hydrogen or alkyl,
R^4 represents substituted alkyl,
R^5 represents alkyl, alkoxy, aryl or aryloxy, each of which can be optionally substituted, or represents amino or $-NR^6R^7$,
R^6 represents hydrogen or alkyl,
R^7 represents hydrogen, alkyl, alkenyl, alkynyl, aryl or aralkyl, each of which can be optionally substituted,
X represents O or S.

4. Process for the preparation of substituted ureas of the formula Ia

Ia

in which
R^1 represents alkyl, one or polycyclic cycloalkyl, cycloalkanone, alkenyl, cycloalkenyl, cycloalkenone, naphthyl or thiophene, each of which can optionally be substituted,
R^2 represents hydrogen or alkyl,
R^3 represents hydrogen or alkyl,
R^4 represents substituted alkyl,
R^5 represents alkyl, alkoxy, aryl or aryloxy, each of which can be optionally substituted, or represents amino or $-NR^6R^7$,
R^6 represents hydrogen or alkyl,
R^7 represents hydrogen, alkyl, alkenyl, alkynyl, aryl or aralkyl, each of which can be optionally substituted,
X represents O or S,

a) in the case where R^2 represents hydrogen, isocyanates or isothiocyanates of the formula II

$$R^1\text{-NCO(S)} \qquad \text{II}$$

in which

R^1 has the abovementioned meaning,

are reacted with amino acid derivatives of the formula III

$$\begin{array}{l} R^3 \quad R^4 \\ | \quad\ | \\ HN - CH - COR^5 \end{array} \qquad \text{III}$$

in which

R^3, R^4 and R^5 have the abovementioned meaning,

where appropriate in the presence of catalysts and diluents, or

b) in the case where R^3 represents hydrogen, amines of the formula IV

$$\begin{array}{l} \quad R^2 \\ \quad | \\ R^1 - N - H \end{array} \qquad \text{IV}$$

in which

R^1 and R^2 have the abovementioned meaning,

are reacted with isocyanates or isothiocyanates of the formula V

$$\begin{array}{l} \quad R^4 \\ \quad | \\ (S)OCN - CH - COR^5 \end{array} \qquad \text{V}$$

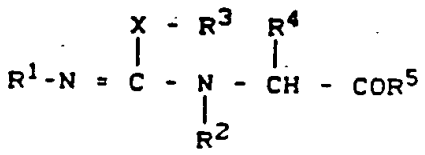
in which

R^4 and R^5 have the abovementioned meaning,

where appropriate in the presence of catalysts

and diluents.

5. Process for the preparation of substituted isoureas of the formula Ib

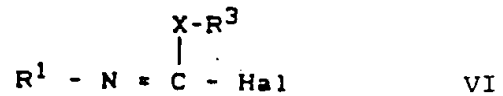


Ib

in which

R^1, R^2, R^3, R^4, R^5, and X have the meaning indicated in Claim 3, and

characterized in that imidocarbonic ester halides of the formula VI

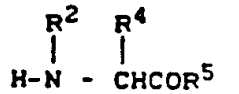


VI

in which

X, R^1 and R^3 have the abovementioned meaning and Hal represents halogen,

are reacted with amino acid derivatives of the formula VII



VII

in which

R^2, R^4 and R^5 have the abovementioned meaning.

6. Growth-promoting agents for livestock, characterized by containing substituted ureas and isoureas of the formulae Ia and Ib according to Claim 1.

7. Feed and feed additives for livestock, characterized by containing substituted ureas and isoureas of the formulae Ia and Ib according to Claim 1.

8. Process for the production of growth-promoting agents, feed and feed additives for livestock, characterized in that substituted ureas and isoureas of the formulae Ia and Ib according to Claim 1 are mixed with vehicles and auxiliaries.

9. A compound according to claim 2 or 3, or a process according to claim 4 or 5 or 8, or an agent according to claim 1 or 6, or an additive according to claim 7, or a method according to claim 1, substantially as herein described with reference to any one of the foregoing examples thereof.

10. Any novel compound, including starting and/or intermediate compounds, set forth herein - or any novel process or method or step thereof set forth herein - the said compound, process, method or step being substantially as herein described.

DATED this 25th day of June 1986

BAYER AKTIENGESELLSCHAFT
By Its Patent Attorneys
ARTHUR S. CAVE & CO.